REMARKS

Claim 18 is directed to a composition comprising a cationic cytofectin as described in Formula I in combination with an exogenous compound for intracellular delivery, said compound being selected from the group consisting of nucleic acids, peptides, peptide derivatives, proteins, protein derivatives, steroids, hormones, carbohydrates, and pharmaceutical compounds, and, optionally, the composition may include a neutral lipid. Claim 18 has been amended to further define the nature of the invention recited therein. In particular, Claim 18 has been amended to incorporate the novel feature of the invention into the body of the claim, namely that the composition disclosed therein *is effective for the intracellular delivery of the exogenous compound in vivo or in vitro*. In addition, Claim 18 has been amended to recite that the exogenous compounds for intracellular delivery according to the invention includes pharmaceutical compounds thereof, i.e., pharmaceutical formulations that include the exogenous compounds listed in Claim 18. Support for this amendment may be found throughout the specification, in particular, page 7, fourth full paragraph and the paragraph bridging pages 7 and 8.

Claims 45 and 46 have been canceled.

No new matter is added by the amendment to Claim 18. Entry of the amendments and allowance of Claims 18-44 are respectfully requested.

I. Issue raised under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 33, 45, and 46 under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner,

> "Claim 33 recites the limitation 'lipid-like molecule' . . . There is insufficient antecedent basis for this limitation in the claim. Furthermore, it cannot be determined how close to the original lipid a 'lipid-like molecule' must be in order to fall within the scope of the claimed subject matter. Thus, the skilled artisan could not determine infringement of the claim, rendering the metes and bounds of the claimed subject matter unclear." (See, Office Action, page 6.)

Applicant asserts that the scope of the term "lipid-like molecule" is clearly defined in the specification and is well understood by one skilled in the art. As disclosed in the specification, a "liposome" according to the present invention denotes a structure comprised of a neutral lipid or

lipid like molecule and a compound according to Formula I. (See, specification, page 5, fourth paragraph.) It is known in the art that the structure of a liposome facilitates its fusion with the plasma membrane. According to the specification,

> "The present invention further provides liposomes comprising (a) a neutral lipid such as dioleoylphosphatidylethanolamine (DOPE) or **similar lipid-like compounds such as** 1,2-dioleoyloxiphosphatidylethanolamine or other lipid-like structures and (b) one or more of the compounds of Formula (I)." (See, specification, page 1, sixth paragraph.) (emphasis added.)

Therefore, one skilled in the art would understand a "lipid-like molecule" as a molecule with a similar structure/function as a known neutral lipid such as DOPE, i.e., a molecule that forms an essential component of a liposome and facilitates its fusion with the plasma membrane.

Reconsideration of the objection under 35 U.S.C. §112, second paragraph and allowance of Claim 33 are respectfully requested.

With respect to Claims 45 and 46, the Examiner states,

> "Claims 45 and 46 recite the limitation 'the DNA/cationic cytofectin (w/w) ratio' in lines 1-2. There is insufficient antecedent basis for this limitation in the claims." (See, Office Action, page 6.)

Claims 45 and 46 have been canceled and this rejection is now moot.

II. Issue raised under 35 U.S.C. §112, first paragraph

The Examiner has rejected Claims 39, 45, and 46 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. According to the Examiner,

> "Claim 39 recites co-lipid molecules linked to the exogenous compound of claim 18 . . . A review of the disclosure as filed, including pages 8 and 9, does not reveal support for linking a cell targeting co-lipid to the exogenous compound."

Claim 39 has been amended to depend from Claim 36 directed to an embodiment of Claim 18 further comprising a cell targeting component. Claim 39 has also been amended to remove the recitation that the neutral co-lipid or negatively charge co-lipid is "covalently linked to the exogenous compound". Support for this amendment may be found in the specification on page 6, fourth paragraph. No new matter is added by the amendment to Claim 39. Entry of the amendment and allowance of Claim 39 is respectfully requested.

With respect to Claims 45 and 46, the Examiner states,

> Claims 45 and 46 recite particular DNA/cationic cytofectin ratios . . . [T]here is no disclosure of any DNA/cationic cytofectin ratios, only DNA/liposome or DNA/lipid ratios . . . thus, the claims contain impermissible New Matter." (See, Office Action, page 7.)

As stated above, Claims 45 and 46 have been canceled and this rejection is now moot.

III. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20 and 23-27 under 35 U.S.C. §102(b) as anticipated by Milieva et al., *J. Appl. Toxicol.*, 15: 219-222 (1995). According to the Examiner,

> "Milieva et al. teach the use of N,N,N'N'-tetramethyl-N,N'-di(8-15-dicloropentadeca-5,10-dien)ethylenediamine methylsulphate in Kreb's solution, which contains glucose (a carbohydrate) and sodium chloride." (See, Office Action, page 3.)

Milieva et al. report on the biphasic effect of a known fungicidal quaternary ammonium salt (QAS), on the mechanical and electrical activity of smooth-muscle samples from rat and guinea pig, i.e., depolarization followed by an increase in spontaneous contractile activity (phase 1) and depolarization followed by inhibition of rhythmic activity (phase 2). (See, for example, page 221, left column.) According to Milieva et al., following removal of the smooth muscle samples, "The samples were **flushed** with a modified Krebs solution." (See, Milieva et al., page 219, right column; emphasis added.) Therefore the Krebs solution referred to by the Examiner is only used to flush the smooth muscle after extraction from the animal and Milieva et al. does not teach or disclose that the QAS compound serves to transport any of the ingredients of the Krebs solution into the cells of the smooth muscle and there is no indication in Milieva et al. that there is any specific association at all between the QAS and the Krebs ingredients referred to by the Examiner, i.e., glucose and/or sodium chloride. Nor is there any indication that intracellular transport of any material inherently occurs.

In fact, there is no disclosure in Milieva et al. at all concerning use of the QAS compound disclosed therein for transfection and no disclosure or suggestion for use of QAS in a composition comprising an exogenous compound, e.g., DNA, protein, etc., whereby the QAS facilitates the intracellular delivery, i.e., transfection, of the exogenous compound. Claim 18 of the present application has been amended to specifically include this feature in the body of the claim, namely

that the composition disclosed therein is effective for the intracellular delivery of the exogenous compound.

Reconsideration and allowance of Claims 18-20 and 23-27 are respectfully requested.

IV. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20, 23-25, and 27 under 35 U.S.C. §102(b) as anticipated by Sykora et al., *Folia Microbiol.*, 36(3): 240-245 (1991). According to the Examiner,

> "Sykora et al. teach the use of BDHD in Luria Broth, or LB medium. Luria Broth comprises peptides and sodium chloride, both of which are within the scope of exogenous compounds in claim 18 . . . Sodium chloride is considered a pharmaceutical compound because it is found in Ringer's solution, itself considered a pharmaceutical that is used intravenously to maintain an isotonic balance with blood." (See, Office Action, page 4.)

The Sykora et al. reference is directed to the analysis of the bactericidal, i.e., plasmid-curing (removal) effect of N,N'-bis (decyldimethyl)-1,6-hexanediammonium dibromide (BDHD) on *E. coli* and *S.typhimurium*.

Sykora et al. report on attempts to cure, i.e., eliminate, six different plasmids from *E. coli* (F'lac, R144, RP4, R6K, R16, and pKM 101) and one plasmid, pKM 101, from *Salmonella typhimurium*, by treatment of the cells with BDHD. According to Sykora et al., bacteria were grown in an overnight culture with the appropriate antibiotic, collected, incubated with fresh antibiotic-free LB plus varying concentrations of BDHD, and plated on agar plus antibiotic to select for colonies with plasmids. The percent of bacterial cells cured of plasmid, i.e., eliminated from the cell, was determined from the proportion of plasmid-less colonies.

However, the Luria Broth cited by the Examiner is simply a widely known and commonly used bacterial growth media that includes glucose and sodium chloride to facilitate growth of the bacteria. There is no teaching or disclosure in Sykora that BDHD complexes with or assists bacteria in the uptake of the glucose and/or sodium chloride from the Luria Broth. In addition, there is no teaching or disclosure in Sykora et al. concerning the use of BDHD or any cationic cytofectin compositions for transfection, i.e., insertion of a foreign compound, e.g., plasmid DNA, into a cell and no disclosure or suggestion for use of BDHD in a composition that includes an exogenous compound, e.g., DNA, protein, whereby the BDHD is capable of intracellular delivery, i.e., transfection of the exogenous compound. Sykora et al. disclose contacting a bacterial cell with a quaternary ammonium salt *only*, i.e., not as a component of a composition, to

remove a native or inserted DNA sequence from the bacterial cell. Also, there is no disclosure in Sykora that BDHD facilitates the transfection of any of the "exogenous" compound ingredients of Luria Broth into the bacterial cell. In fact, Applicants assert that one skilled in the art, after reviewing this reference, could only conclude that the disclosure of Sykora et al. actually teaches away from Applicants' claimed composition for inserting a foreign molecule into a cell.

And, in addition, Applicants assert that one skilled in the art would not look to the teaching of Sykora et al. to formulate the composition of the present invention for intracellular delivery of an exogenous compound via the disclosed composition. Sykora et al. provide no teaching and no suggestion that a compound for specifically eliminating a plasmid from a dividing, gram negative, prokaryotic bacterial cell would be useful in a novel composition for inserting a plasmid, or any other compound, into a cell.

However, Applicants have amended Claim 18 of the present application to specifically include in the body of the claim, the novel feature that the composition of the present invention is effective for the intracellular delivery of the exogenous compound included in the composition.

Reconsideration and allowance of Claims 18-20, 23-25, and 27 are respectfully requested.

V. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20, 23-25, and 27 under 35 U.S.C. §102(b) as anticipated by Squibb, GB1277086. According to the Examiner,

> "The '086 document discloses the use of hexamethylenebis-(n-decyldimethyl-ammonium)dibromide, hexamethylenebis-(n-dodecyldimethyl-ammonium)dibromide, hexamethylenebis-(n-octyldimethyl-ammonium)dibromide, hexamethylenebis-(n-nonyldimethyl-ammonium)dibromide, and hexamethylenebis-(n-undecyldimethyl-ammonium)dibromide. These compounds may be used in conjunction with a surface active agent, such as sodium lauryl sulfate . . . Sodium lauryl sulfate is considered a pharmaceutical compound because of its use in shampoos, toothpastes and pharmaceutical preparations." (See, Office Action, page 4.)

Squibb discloses these compounds only for use as foliage fungicides and aquatic herbicides,

> "This invention relates to novel hexamethylenebis (alkyldimethylammonium)bromides and their use as foliage fungicides and aquatic herbicides." (See, Squibb, left column, second paragraph.)

There is no disclosure in Squibb concerning use of the quaternary ammonium salts disclosed therein for transfection and no disclosure or suggestion for use of the quaternary

ammonium salts in a composition further comprising an exogenous compound, e.g., DNA, protein, etc., whereby the composition is capable of intracellular delivery, i.e., transfection, of the exogenous compound.

However, Claim 18 has been amended to recite that the exogenous compounds suitable for intracellular delivery according to the present invention include nucleic acids, peptides, peptide derivatives, proteins, protein derivatives, steroids, hormones, carbohydrates, and pharmaceutical compounds thereof. As such, sodium lauryl sulfate is not included in this list of exogenous compounds recited in Claim 18.

Reconsideration and allowance of Claims 18-20, 23-25, and 27 are respectfully requested.

VI. Nonstatutory Obviousness-Type Double Patenting

The Examiner has maintained the nonstatutory obviousness-type double patenting rejection against Claims 18-26 and 28-32, and included new Claims 33-46, as being unpatentable over Claims 1-8 and 11-46 of U.S. Pat. No. 6,733,777. The Examiner indicates that a terminal disclaimer in compliance with 37 C.F.R. §§1.321(c) or 1.321(d) may overcome this rejection.

Applicants acknowledge the double patenting rejection made by the Examiner. However, Applicants assert that the composition claims as amended above clearly distinguish these claims as a separate invention from the method claims of U.S. Pat. No. 6,733,777. Applicants assert that the above-referenced claim amendments obviate the requirement for a terminal disclaimer in the present application.

Applicants note that a Restriction Requirement issued in July 2001 (paper no. 15) in the parent application that eventually became U.S. Pat. No. 6,733,777, made of record that claims directed to cationic cytofectin compounds for delivering exogenous compounds into cells (Group I) covered separately patentable subject matter from claims directed to methods of delivering exogenous compounds into cells using the cationic cytofectins and liposomes comprising the cationic cytofectins (Group II). Applicants elected, with traverse, the claims of Group II for further prosecution in the parent case. Therefore, subject matter which was deemed separately patentable in the application that eventually issued as the '777 patent, can not now form the basis for a double patenting rejection of subject matter that was restricted out of that application and carried forward for examination in the present divisional application. The Examiner's reason for maintaining the rejection (incorporated by reference to the previous action) does not apply, because in the parent application the Group I claims were amended to the format of method

claims belonging to elected Group II. The Examiner vacated the restriction because no claims were left in the format of Group I.

Withdrawal of the double patenting rejection and allowance of Claims 18-26, 28-38, and 40-44 are respectfully requested.

Allowance of Claims 18-44 are respectfully requested.

Respectfully submitted,

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date

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